Title: Motor cortical responses following short-term strength training: a systematic review and meta-analysis

Running head: Strength training and cortical plasticity

Author names: Dawson J Kidgell[1], Daniel R Bonanno[2], Ashlyn K Frazer[1], Glyn Howatson[3,4], Alan J Pearce[5,6]

Author affiliations:

[1] Discipline of Exercise Science, School of Allied Health, La Trobe University, Melbourne, Australia.

[2] Discipline of Podiatry, School of Allied Health, La Trobe University, Melbourne, Australia.

[3] Faculty of Health and Life Sciences, Northumbria University, Newcastle-upon-Tyne, UK

[4] Water Research Group, School of Environmental Sciences and Development, Northwest University, Potchefstroom, South Africa.

[5] Faculty of Health, Arts and Design, Swinburne University of Technology, Melbourne, Australia.

[6]Melbourne School of Health Sciences, Faculty of Medicine, Dentistry and Health Science, The University of Melbourne, Australia.

Authors' contributions

All authors were fully involved in the preparation of the study protocol. DJK, AJP, AKF and GH were responsible for the preparation of the manuscript, DRB was responsible for data analysis, and all authors were involved in its review prior to submission for publication. The material within has not been and will not be submitted for publication elsewhere. All authors read and approved the final manuscript.

Corresponding author details:

Dawson J. Kidgell, PhD

Discipline of Exercise Science, School of Allied Health, La Trobe University, Melbourne, Australia

Phone: +61 3 9479-3713

Email: D.Kidgell@latrobe.edu.au

Abstract

Background: Strength training results in adaptive changes in skeletal muscle, however, adaptive changes in the central nervous system also occur. Over the last 15 years, non-invasive brain stimulation techniques, such as transcranial magnetic stimulation, have been used to study the neural adaptations to strength training. The present review explored the working hypothesis that the early neural adaptations to strength training may in fact be due to changes in corticospinal excitability and inhibition and, such changes, contribute to the early gain in strength following short-term training.

Methods: A systematic review, according to PRISMA guidelines identified studies by database searching, hand-searching and citation tracking in August 2016. Methodological quality of included studies was determined using the Downs and Black quality index. Data were synthesised and interpreted from meta-analysis.

Results: Twenty studies investigating the corticospinal responses following strength training were included. Meta-analysis found that short-term strength training increased strength (standardized mean difference [SMD] 0.76, 95% CI 0.46 to 1.06) and decreased corticospinal inhibition (SMD -0.53, 95% CI -0.93 to -0.13). Short-term strength training had no effect on motor threshold (SMD -0.12, 95% CI -0.49 to 0.25), corticospinal excitability (SMD 0.23, 95% CI -0.10 to 0.56) or short-interval intracortical inhibition (SMD -0.90, 95% CI -1.86 to 0.07).

Conclusion: The corticospinal response to short-term strength training is characterised by a reduction in corticospinal inhibition, rather than an increase in corticospinal excitability. These data demonstrate that strength training targets intracortical inhibitory networks within the corticospinal tract and which characterizes an important neural adaptation to strength training.

New & Noteworthy:

This systematic review and meta-analysis shows that a 'new' early neural adaptation to strength training is a reduction in corticospinal inhibition and not an increase in corticospinal excitability. A reduction in corticospinal inhibition results in an increased net drive to the motor neuron pool and appears to accompany the early gain in strength.

Key words: Corticospinal, excitability, inhibition, strength training, transcranial magnetic stimulation.

Introduction

Strength can be broadly defined as the maximal force or torque that can be developed by the muscles performing a specific movement. It has been demonstrated that training-related changes in muscle strength are accompanied by adaptive alterations in the neuromuscular system during the early phases of a strength training program (Enoka 1988; Carroll et al. 2002). Evidence for changes in the central nervous system (CNS) following strength training has been provided through the use of surface electromyography (sEMG), evoked spinal reflex recordings, and via single motor unit recordings (Narici et al. 1989; Duchateau et al. 2006; Del Balso and Cafarelli 2007). Changes in the amplitude of the sEMG signal have, by default, been interpreted as increases in neural drive, therefore contributing to the increase in force production (Davies et al. 1985; Narici et al. 1989). Measurement of evoked spinal reflexes, such as the Hoffman reflex (H-Reflex) and volitional wave (V-wave) have also been shown to increase following a period of strength training, possibly contributing to early strength development (Aagaard et al. 2002; Del Balso and Cafarelli 2007; Fimland et al. 2009).

At the cortical level, adaptive changes in the primary motor cortex (M1) may also contribute to the early phase of strength development (Carroll et al. 2002; Griffin and Cafarelli 2007; Kidgell and Pearce 2010). One of the most robust tools available to study the function of the M1 is the technique of transcranial magnetic stimulation (TMS) (Chen 2000; Hallett 2000). Briefly, TMS involves a transient magnetic field that induces an electrical field in a relatively focal area of the brain. TMS can be applied as single-pulse, or paired-pulse, stimulation over the M1. Single-pulse stimulation over the M1 can induce a series of descending volleys (i.e., action potentials) in the corticospinal pathway which, in turn, cause a muscle response referred to as a motor evoked potential (MEP; Figure 1).

<Insert Figure 1 here>

Several variables are used to measure the excitability of the motor cortical pathway. Motor threshold simply denotes the minimum stimulation intensity that is required to evoke a MEP in the target muscle when single-pulse stimuli are applied to the M1. Many studies use the criterion level for establishing motor threshold based upon the amplitude of the TMS evoked MEP being more than 50 μV peak-to-peak in amplitude in at least 50% of successive trials in resting muscles, or greater than 200 μV in slightly-contracted target muscles (Rossini et al. 1994). Physiologically, the motor threshold represents the membrane excitability of corticospinal neurons and interneurons projecting onto these neurons in the M1, as well as the excitability of motor neurons in the spinal cord, neuromuscular junction and the muscle itself (Rossini et al. 1994). In addition, motor threshold provides important information about the efficacy of a chain of synapses from presynaptic cortical neurons to the target muscle. Interestingly, higher motor thresholds are associated with reduced M1 excitability, whilst lower thresholds are associated with increased M1 excitability. Further, it is well known that various interventions or events can alter an individual's motor threshold. For example, motor skill training has been shown to reduce motor threshold (Pascaul-Leone et al. 1995), and reported motor thresholds are different between hemispheres in patients who have suffered a stroke (Byrnes et al. 1999; Byrnes et al. 2001).

The amplitude of the MEP reflects the integrity of the corticospinal pathway and the excitability of the M1, and the efficacy of conduction along the peripheral motor pathway (Hallett 2000). When controlled for torque and type of motor task, the MEP is a reliable intra-participant measure (Kamen 2004; van Hedel et al. 2007) allowing for confident interpretation of changes following acute or chronic interventions (Carson et al. 2013). Adjustments in MEP amplitude are thought to reflect changes in the strength of corticospinal cell projection onto spinal motor neurons innervating target muscles.

Although the MEP amplitude is reflective of the excitability of corticospinal cell projection, changes in corticospinal inhibition may also be important for voluntary muscular activity and, therefore, a potential mechanism underpinning changes in strength development (Kidgell and Pearce 2011). When supra-threshold single-pulse TMS is applied over the contralateral M1 whilst a participant is maintaining a low-level muscle contraction, there is a pause in the on-going sEMG signal, referred to as the cortical silent period (cSP; Figure 1), which can last up to a few hundred milliseconds (Wilson et al. 1993). The duration of the cSP is believed to be due to inhibitory mechanisms at the level of the M1, while spinal inhibitory mechanisms such as Renshaw cell inhibition are thought to contribute only to the first 50-60 ms (Fuhr et al. 1991; Wilson et al. 1993). The duration of the cSP is most likely mediated by γ-Aminobutyric acid B ($GABA_B$) receptors (Werhahn et al. 1999). However, a limitation of single-pulse TMS is that it activates corticospinal cells trans-synaptically and, therefore, does not provide any information about the effect of intracortical inhibitory inputs onto corticospinal cells (Hallett 2000). Conversely, paired-pulse TMS can be used to assess the effect of an exercise intervention on the intracortical inhibitory and/or excitatory connectivity confined with the M1.

Paired-pulse TMS allows an objective assessment of the motor cortical responses, such as neural plasticity and altered synaptic activity confined to the M1 in response to various tasks and disorders (Hallett 2000). When a sub-threshold conditioning stimulus precedes a supra-threshold test stimulus by a time interval (inter-stimulus interval; ISI) of less than 5 ms, it results in suppressed MEPs compared with those from single-pulse stimuli at the same intensity (Kujirai et al. 1993) (Figure 2). The conditioning stimulus activates low-threshold inhibitory circuits that use the neurotransmitter γ-Aminobutyric acid A ($GABA_A$), resulting in synaptic inhibition of corticospinal cells targeted by the supra-threshold test stimulus (Ni and Chen 2008; Petersen et al. 2010). The ratio between the amplitudes of the paired-pulse and

single-pulse MEPs represents short-interval intracortical inhibition (SICI). Two distinct phases of inhibition have been described: one that occurs with an ISI of 1 ms, and one with an ISI of 2-4 ms. Little is known about the inhibition at 1 ms; however, it is now accepted that the inhibition occurring at an ISI of 2-4 ms is synaptic in origin, mediated by GABAergic inhibitory neurons acting via $GABA_A$ receptors (Kujirai et al. 1993; Müller-Dahlhaus et al. 2008; Vucic et al. 2009).

<Figure 2 here>

There are now many studies that have employed TMS to investigate the integrity of the motor cortical pathway under experimental conditions, as well as in health and disease. Specifically, with regards to strength training, emerging studies are exploring motor cortical responses, such as corticospinal excitability and inhibition, following short-term (< 4-wks) training interventions (Beck et al. 2007; Griffin and Cafarelli 2007; Lee et al. 2009; Kidgell and Pearce 2010; Coombs et al. 2016). One of the first studies using TMS to investigate the motor cortical responses following strength training (Carroll et al. 2002) observed that short-term strength training of the first dorsal interosseous (FDI) muscle, despite reporting a large increase in muscle strength following training, did not alter the size of the MEP at rest, or at higher force levels; rather, a significant reduction in MEP amplitude was observed. Similarly, Jensen et al. (2005) reported a significant reduction in the size of the maximal MEP and slope of the stimulus-response curve at rest following 4-wks strength training of the Biceps Brachii (BB) muscle. Further, Lee et al. (Lee et al. 2009) observed that 4-wks of strength training of the wrist abductors did not modify the size of the TMS evoked MEP. More recently, Coombs et al. (2016) showed that 3-wks of wrist extensor strength training had no effect on corticospinal excitability, despite significant increases in muscle strength. However, in contrast, Griffin and Cafarelli (2007) observed a 32% increase in MEP amplitude following isometric strength training of the tibialis anterior (TA). More recently, strength training of

both the upper and lower limbs, which is paced to an audible metronome, has consistently demonstrated increases in MEP amplitude following isotonic strength training (Kidgell et al. 2010; Kidgell et al. 2011; Weier et al. 2012; Pearce et al. 2013; Leung et al. 2015).

Whilst the MEP amplitude has provided equivocal findings, changes in corticospinal inhibition appear to be more robust. This suggests that an important neural adaptation that might underpin the rapid increase in strength following short-term strength training could be a reduction in corticospinal inhibition. Recently, several studies in both healthy younger and older adults have reported that the duration of the cSP is reduced following isometric and isotonic strength training (Kidgell and Pearce 2010; Kidgell et al. 2011; Latella et al. 2012; Christie and Kamen 2013; Hendy and Kidgell 2013; Coombs et al. 2016). At the very least, these results are suggestive that strength training targets specific populations of intracortical neurons that are $GABA_B$ sensitive, which manifests as an increase in neural drive to the trained muscle.

As TMS studies following short-term strength training are an emerging, but nonetheless a growing area of research, the body of evidence is largely equivocal and, therefore, a systematic review with meta-analysis will serve to clarify the status quo within the literature. The present review examines the working hypothesis that the early motor cortical responses to strength training are due to changes in corticospinal excitability and inhibition. Such changes underpin the early gain in strength following short-term training. The specific aim of this study was to conduct a systematic review of the literature and meta-analysis to examine the motor cortical responses following short-term strength training.

Material and Methods

This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al. 2009).

Inclusion and exclusion criteria

Articles were eligible for inclusion if they included: (i) Healthy young humans (male and female) between the age of 18 and 40 years; (ii) training intervention involved was stated to include strength training of a duration between two and eight weeks, resistance training, or stability training; and (iii) stimulation of M1 to quantify changes in excitability with MEPs or paired-pulse measures (such as ICF), and inhibition using cSP duration or paired-pulse measures (such as SICI and/or LICI). Exclusion criteria established for searches included: (i) diseased population groups; (ii) non-English publications (as no translation services were available); (iii) non-peer or limited review conference proceedings; (iv) conference abstracts; (v) books; and (vi) theses (e.g. PhD, Masters and Honours).

Search strategy

A standardised search strategy (see Table 1) used the following electronic databases: Cochrane Library, CINAHL, EMBASE, MEDLINE complete, PsycINFO, PubMed, Science Direct, SciVerse SCOPUS, Sport Discus, and Web of Science. Databases were searched using combinations of variants of the following terms: “transcranial stimulation”, “transcranial magnetic stimulation”, “TMS”, “repetitive paired-pulse”, “motor cortex”, “motor evoked potentials”, “cortical silent period”. All reference lists of included articles were searched and appropriate papers included. Search dates were between January 1990 and the first week of August 2016.

<Table 1 here>

Two authors (AJP and DJK) independently screened the titles and abstracts of returned articles, excluding any articles that were duplicates or violated inclusion criteria. Any discrepancies where resolved through consensus or consultation with a third author (AKF). Full-text articles were obtained and exported with their citation to Endnote (Version X7.1, Thompson Reuters), with no hand entering or modifying references. Figure 3 summarizes the flowchart of studies removed following application of each criterion according to the PRISMA guidelines. Although PRISMA guidelines are usually employed to report on randomized trials, PRISMA can also be used for systematic reviews reporting quasi-experimental research (Moher et al. 2009; Kidgell et al. 2016).

Methodological quality assessment

One reviewer (AJP) independently assessed the quality of the included studies (Table 2) using the Downs and Black checklist (Table 2) (Downs and Black 1998). This checklist assesses randomized and non-randomized quasi-experimental research designs. It scores 27 items (up to a maximum of 32 points with Questions 5 and 27 scoring up to 2 points and 5 points, respectively) through a rating of 1 for 'yes', or 0 for 'no' or 'unable to determine', indicating the quality of interventions and outcome measures of the studies. Summed scores closer to 32 points are reflective of superior quality of the study, thereby increasing the confidence in conclusions (Downs and Black 1998). Risk of bias (high, low, or not applicable) was assessed using the Cochrane Collaboration Risk of Bias Tool (Higgins et al. 2011) (Table 3). This tool evaluates the risk of investigator bias in the selection, performance, detection, attrition, and reporting of the individual studies included in this review.

Assessment of evidence level was conducted using the National Health and Medical Research Council (NHMRC) guidelines for the evaluation of research (Council 1999). The

levels of evidence range from Level I (highest), with data obtained from a systematic review of all randomized controlled trials, through to Level IV from case series material (Table 2).

<Table 2 here>

<Table 3 here>

Data analysis

Data from each study were extracted from the available text. Outcome measures included: motor threshold (MT), expressed as a percentage of maximal stimulator output; MEP amplitude (peak to peak waveform and expressed either as a raw amplitude or percentage of peripheral M-wave amplitude (Sandbrink 2008)); and cortical silent period, quantified as the duration from the onset of MEP waveform to the return of uninterrupted EMG activity (Wilson et al. 1993; Wolters et al. 2008)). The only paired-pulse measure that was included in the meta-analysis was SICI, which was quantified as the ratio of the test stimulus and conditioning stimulus (Kujirai et al. 1993).

Where the reported data were not sufficient for the purposes of this review, the corresponding author of the study was contacted and relevant data were requested. Meta-analysis was calculated using the Cochrane Collaboration Review Manager 5.3 software. The pre- and post-strength training data were used from each study for the following variables: strength, MT, MEP excitability, cSP inhibition and SICI. A random-effects model was used for the meta-analyses as it was assumed that the intervention effects would vary among the included studies due to differences between the study design, interventions, participants and researchers (Borenstein et al. 2010). Standardized mean differences (SMD) with 95% confidence intervals were used to measure the intervention effect for all outcomes. Statistical heterogeneity of the included studies was calculated using the I^2 statistic, where <25%

indicates low risk of heterogeneity, 25 to 75% indicates moderate risk of heterogeneity and >75% indicates high risk of heterogeneity (Higgins et al. 2003).

Results

Figure 3 illustrates the flow of studies through the systematic review process. The initial search yielded 3,500 titles and abstracts. Following removal of duplicates, the titles and abstracts of the remaining 961 records were screened; 864 publications were removed as these publications did not meet eligibility criteria. Ninety-seven full-text articles were assessed for eligibility, with a further 66 of these being removed for a number of reasons outlined in Figure 3. Thirty-five papers were examined (31 from the initial analysis and a further four identified through the internet search); however, 15 were not included in the final analysis despite meeting the criteria. Reasons for their exclusion were that the study analysed the effects of a single training session or non-training cross-sectional study comparing well-trained versus novice or non-trained individuals, all of which did not meet the criteria of the primary research question focusing on adaptation of multiple training sessions.

Quality assessment

The specific details of included studies, incorporating the Downs and Black quality assessment and NHMRC assessment of evidence for each study, are provided in Table 2. All but one study, which did not have a parallel control group (Fisher et al. 2016), were comparative studies having a concurrent control condition (NHMRC study evidence guidelines Grade III-1 or III-2, Table 2).

The Downs and Black checklist for study quality revealed that the included studies ranged between 12 and 19 (out of 32 points), with a mean score of 17.4 (SD 1.8) (Downs and Black 1998). This indicated a ‘low to moderate’ quality of research across the studies. It is important to note, however, that this checklist is predominantly used for randomized control trials and intervention studies (Downs and Black 1998). Consequently, studies lost points not only for being statistically underpowered but also due to not revealing sampling recruitment,

descriptions of randomization, blinding of participants and blinding of those measuring outcomes.

The risk of bias analysis (Table 3) revealed 'moderate-to-high' risk bias for the majority of studies (Higgins et al. 2011). Moreover, half of the studies were identified to be from the one laboratory group, suggesting the potential for further risk of bias.

Strength

The pre- and post-training strength data from 17 studies investigating the effects of short-term strength training on motor cortical responses were pooled, with five yielding results indicating increased strength post-training. The remaining 12 studies demonstrated no change in pre- and post-training strength. The pooled data from the 17 studies indicated that short-term strength training produces an increase in strength (SMD 0.76, 95% CI 0.46 to 1.06), with heterogeneity of results between the studies being moderate (I^2 = 41%; Figure 4).

<Figure 4 here>

Motor threshold

The pre- and post-training MT data from 12 studies investigating the effects of short-term strength training on motor cortical responses were pooled, with one study indicating a decrease in MT post-training. The remaining 11 studies demonstrated no change in pre- and post-training MT. The pooled data from the 12 studies indicated that short-term strength training produces no effect on MT (SMD -0.12, 95% CI -0.49 to 0.25), with heterogeneity of results between the studies being moderate (I^2 = 48%; Figure 5).

<Figure 5 here>

MEP excitability

The pre- and post-training MEP excitability data from 20 studies investigating the effects of short-term strength training on motor cortical responses were pooled. Three studies yielded results indicating increased MEP excitability and one study found a decrease in MEP excitability post-training. The remaining 16 studies demonstrated no change in pre- and post-training MEP excitability. The pooled data from the 20 studies indicated that short-term strength training produces no effect on MEP excitability (SMD 0.23, 95% CI -0.10 to 0.56), with heterogeneity of results between the studies being moderate (I^2 = 62%; Figure 6).

<Figure 6 here>

cSP inhibition

The pre- and post-training cSP inhibition data from seven studies investigating the effects of short-term strength training on motor cortical responses were pooled, with three yielding results indicating decreased cSP inhibition post-training. The remaining four studies demonstrated no change in pre- and post-training cSP inhibition. The pooled data from the seven studies indicated that short-term strength training produces a decrease in cSP inhibition (SMD -0.53, 95% CI -0.93 to 0.13), with heterogeneity of results between the studies being moderate (I^2 = 36%; Figure 7).

<Figure 7 here>

SICI

The pre- and post-training SICI data from six studies investigating the effects of short-term strength training on motor cortical responses were pooled, with two studies yielding results demonstrating a decreased SICI post-training (Beck et al. 2007; Weier et al. 2012). The remaining four studies demonstrated no change in pre- and post-training SICI. The pooled

data from the six studies indicated that short-term strength training produces no effect on SICI (SMD -0.90, 95% CI -1.86 to 0.07), with heterogeneity of results between the studies being high (I^2 = 82%; Figure 8).

<Figure 8 here>

Discussion

This systematic review and meta-analysis aimed to estimate the motor cortical responses following short-term strength training, specifically examining the idea that adaptive changes in corticospinal excitability and inhibition contribute to the early phase of strength development (Carroll et al. 2002). Overall, this review found: (1) there was a medium-large effect (SMD = 0.76) on increasing strength; (2) strength training did not change MT or MEP amplitude; and (3) in studies that included corticospinal inhibition, there was a medium effect (SMD = -0.53) on reducing cSP and there was no overall effect on SICI. Despite these important findings, the quality assessment of studies to date revealed that the studies were of 'low to moderate' quality with an associated 'moderate to high' risk of bias. Therefore, future studies will need to address methodological improvements, especially blinding of post-training TMS data collection to reduce potential bias.

Strength

During the early stages of strength training, it is axiomatic that the gain in muscle strength occurs too rapidly to be explained solely by muscle-based mechanisms. Therefore, it was not surprising that all studies showed an increase in muscle strength following short-term strength training. The data showed a medium-large effect on increasing strength, with studies ranging from six sessions over 2-wks to 16 sessions over 4-wks.

The early muscle strength gains that occur after strength training are thought to predominantly involve neural adaptations, however, the exact locus of adaptation within the central nervous system (CNS), remains unresolved. Although previous studies have reported changes in motor unit behavior, such as increased sEMG amplitude, increased discharge rate, doublet firing of motor units, reduced co-activation of antagonists and increased descending drive (i.e., changes in V-wave amplitude), representing modulation at multiple points along the neuroaxis (Sale 1988), however, the specific role of the M1 underpinning strength training is more elusive (Carroll et al. 2011).

It has recently been proposed that the concept of use-dependent cortical plasticity of neural networks may be similar between skill training and strength training. For example, neural adaptations have been shown to be the preliminary step that improves the acquisition of motor skills (Pascaul-Leone et al. 1995). Particularly in humans, long-term potentiation (LTP) is considered to occur at existing synapses during the early stages of skill acquisition (Rosenkranz et al. 2007). In a similar manner, it has been proposed that strength training may also lead to LTP, and such changes in synaptic activity within the M1 could underpin the rapid gain in strength (Carroll et al. 2002; Selvanayagam et al. 2011). However, to date, it is unclear whether the early neural adaptations that occur following strength training involve a similar mechanism to skill training (Jensen et al. 2005; Leung et al. 2015).

Although the present meta-analysis showed a significant improvement in the trained-muscles ability to generate force, the mechanism modulating force development is not entirely clear. Despite this, reduced intracortical inhibition, rather than increased corticospinal excitability, appears to be an important factor in the acquisition of strength. This implies that strength training regulates specific intracortical inhibitory neurons confined to the M1.

MEP threshold and excitability

For some time, it has been suggested that one potential site of neural adaptation that may underpin the rapid gain in muscle strength is the M1. Certainly, motor skills that require greater dexterity have consistently demonstrated cortical plasticity within the M1, with increased MEP amplitudes and a reduction in intracortical inhibition (Classen et al. 1998; Muellbacher et al. 2001; Muellbacher et al. 2002; Garry et al. 2004). Conversely, relatively few studies have examined the motor cortical responses to strength training (Kidgell and Pearce 2011).

Of particular importance, this meta-analysis found no changes in motor cortical excitability following strength training. Unlike motor skill training, strength training did not alter motor threshold. On this basis, strength training does not affect membrane excitability of corticospinal neurons and interneurons within the M1. Given that motor threshold is representative of synaptic efficacy of presynaptic neurons within the M1 to the target muscle, it is not surprising that corticospinal excitability did not increase at, or above, threshold.

In effect, the results of the meta-analysis add to the literature by showing that strength training does not result in a training-related increase in corticospinal excitability. Although several TMS strength-training studies have shown that MEP amplitude increases (Griffin and Cafarelli 2007; Kidgell et al. 2011; Weier et al. 2012; Pearce et al. 2013), overall, the effects on corticospinal excitability are inconsistent (Carroll et al. 2002; Jensen et al. 2005; Kidgell and Pearce 2010). For example, in the current meta-analysis, three studies reported increased corticospinal excitability (Griffin and Cafarelli 2007; Kidgell et al. 2011; Weier et al. 2012; Pearce et al. 2013), two studies reported a decrease in corticospinal excitability (Carroll et al. 2002; Taube et al. 2007) and the remaining 15 studies showed no change in corticospinal excitability. This finding supports the previous inconsistencies in the literature; however,

potential reasons for the inconsistent findings were related to different strength tasks performed during training (static vs. dynamic, tonic vs. ballistic, etc.), the duration of the training intervention, and/or different methodological techniques. Furthermore, TMS-evoked MEPs assessed at rest might differ from adaptations measured during light activity of the target muscle. Overall, it seems that the previous TMS strength-training literature suggested that there may be a differential effect of strength training on corticospinal excitability, depending on the factors discussed above. However, the current meta-analysis, using SMD, establishes that the overall effect of strength training on modulating corticospinal excitability is not significant.

Based upon the current literature, the overall conclusion would suggest that strength training does not alter corticospinal excitability or the efficacy of neural transmission along the peripheral motor pathway. Given that only two studies included a paired-pulse protocol to investigate intracortical facilitation (Beck et al. 2007), further research using paired-pulse approaches to elucidate the cortical mechanism associated to strength training is required.

Cortical inhibition

Although the previous TMS and strength-training literature showed inconsistencies in corticospinal excitability underpinning the rapid gain in muscle strength, unfortunately, very few studies have examined the potential role of intracortical inhibitory mechanisms that may affect muscle strength. The present review showed for the first time that short-term strength training modulates corticospinal inhibition and this appears to be an important early neural adaptation to strength training. When the data from the seven studies were pooled in the meta-analysis, the overall finding was that strength training produces a medium effect on reducing corticospinal inhibition. As the duration of the silent period is thought to be modulated by $GABA_B$ mediated inhibition (Werhahn et al. 1999) confined within the M1, it

seems that strength training targets specific intracortical inhibitory neurons that collectively results in an increased net drive to the spinal motor neuron pool, which mechanistically manifests as an increase in muscle strength. This is an important new finding that shows a reduction in corticospinal inhibition is important for the increase in muscle strength.

It has been known for some time that the activity of cortico-motoneuronal cells increase linearly with increased force production (Cheney and Fetz 1980; Ashe 1997). However, the M1, and potentially other cortical regions, are rarely recognised as being involved in the determination of muscle strength. Nevertheless, recently, in humans it has been shown that the M1 is a critical determinant of muscle strength (Kidgell and Pearce 2011). To further support the role of the M1 and, in particular, corticospinal inhibition in muscle strength, several experiments that have used a model of immobilization have reported an increased cSP duration and a reduction in muscle strength (Clark et al. 2008); however, motor training seems to attenuate the prolongation of the cSP (Clark et al. 2014).

The current finding of reduced cSP following strength training suggests that the M1 is not only critical for motor coordination and skill acquisition (Karni et al. 1998) but is also important for maximal force generation of individual muscles, and that reduced corticospinal inhibition is mechanistically associated with muscle strength (Kidgell and Pearce 2010; Weier et al. 2012; Christie and Kamen 2013; Coombs et al. 2016). However, we cannot confidently propose that that the reduced cSP is not indicative of changes at a cortical level, given that the duration of cSP is dependent on the intensity of TMS stimulation, and the initial 50 ms is thought to result from spinal mediated mechanisms, with the latter part caused by the activation of long-lasting $GABA_B$-mediated inhibition (Kobayashi and Pascual-Leone 2003; McDonnell et al. 2006; Reis et al. 2008). The current finding, however suggested that the reduced cSP is an important early neural adaptation to strength training. Notably, our interpretation of reduced corticospinal inhibition is consistent with findings from other

studies that have used the paired-pulse TMS technique to specifically probe the intracortical circuitry of the M1 and while measuring muscle strength (Clark et al. 2010; Weier et al. 2012).

Whilst it is not entirely clear why strength training specifically reduces the cSP duration, one working hypothesis is related to the type of strength training or contraction mode used during training. For example, it has been shown that muscle contraction results in sensory feedback (from muscle afferents) which reduces intracortical inhibition (Brerro□Saby et al. 2008; Vie et al. 2013). TMS studies have revealed that the motor cortical responses to lengthening and shortening contractions are different (Sekiguchi et al. 2003; Gruber et al. 2009; Howatson et al. 2011); specifically, the duration of the cSP is reduced during lengthening contractions compared to shortening (Inghilleri et al. 1993), and intracortical inhibition (ICI) is reduced during forceful contractions (Howatson et al. 2011). Irrespective of this, dynamic contractions and isometric contractions increase sensory feedback (from Group III and IV afferents) to supraspinal regions (Gandevia and Burke 1990), so it is likely that persistent sensory feedback as a result of strength training (that utilise shortening and lengthening contractions) results in repeated input to the M1, which modifies corticospinal inhibition. Alternatively, given that forceful contractions increase motor neuron activation, it may simply be that increased motor neuron excitation occurs as a result of reduced inhibition within corticospinal neurons due to repetitive high-force muscle contractions.

Limitations and considerations for further research

Although this systematic review and meta-analysis have identified that short-term strength training results in a reduction in corticospinal inhibition, which appears to be an important 'early' neural adaptation to strength training, there are limitations that must be considered when interpreting the findings.

Firstly, the quality of the study designs is low, for a number of reasons that are not necessarily easy to overcome. A large number of the studies have a small sample size which greatly reduces the power of the data. However, a simple approach to improve the quality of the data and overall design of the studies would be to include more robust TMS techniques, such as paired-pulse measures, to probe specific intracortical circuits of the M1. In the current systematic analysis, only five studies assessed SICI, whilst only two studies assessed ICF, and there have been no studies to date that have examined LICI following strength training. Thus, the current data is of low quality as specific intracortical circuits in the M1 have not been adequately probed. Despite the small sample size reported in most studies, the overall quality could be improved through better blinding of data collection and analysis. For example, blinding the pre- and post-training TMS testing by having experimenters blinded to the conditions, and also having independent data analysis (with inter-rater reliability) for measurement of MEP waveforms, particularly with the analysis of cSP duration given that many software programs can now automatically determine MEP amplitudes.

Although previously it had been thought that a major limitation in understanding the corticospinal responses to strength training was methodological disparity (for example, differences in strength training interventions, the muscle trained, etc.), it is not the only limitation. Regardless of the muscles trained or the type of strength training performed (isometric or dynamic), if the fundamental purpose of strength training is to increase strength, then the CNS must adjust by increasing the activation of the spinal motor neuron pool that contributes to strength development. To this end, a limitation within the research to date has been the recording of MEPs from an agonist muscle only. Such an approach likely lacks the sensitivity to detect any meaningful adjustment in corticospinal excitability and changes in motor neuron activation in the antagonist and synergistic muscles that also contribute to force development. Certainly, TMS studies should examine the potential adjustment in MEPs from

synergist and antagonist muscles that produce force in the training direction. There is a pressing need to examine other elements of corticospinal excitability, such as TMS-evoked twitch forces, cervico-medullary evoked potentials, and changes in intra-cortical excitability such as short-interval intracortical inhibition, short-interval intracortical facilitation, long-interval intracortical inhibition and intracortical facilitation.

Conclusions

The findings from this systematic review and meta-analysis demonstrate that short-term strength training results in a reduction in intracortical inhibition. Interestingly, although the excitability of the M1 is thought to modulate the acquisition of newly formed motor skills, strength training does not appear to modulate corticospinal excitability; rather, it modifies corticospinal inhibition. Given that the duration of the cSP is primarily of a cortical origin, this meta-analysis indicates that short-term strength training results in adaptive changes at the supraspinal level. This is an important new finding that illustrates that an 'early' neural adaptation to strength training is the removal of intracortical inhibition from the M1 that mechanistically increases muscle strength. However, there is a need for further studies to be conducted that use paired-pulse protocols to probe the intracortical circuitry of the M1, specifically, the effect of strength training on short-interval and long-interval intracortical inhibitory circuits along with intracortical facilitatory circuits.

Conflicts of interests

All authors declare that they have no conflicts of interest that are relevant to the content of this review.

References

Aagaard P, Simonsen EB, Andersen JL, Magnusson P, and Dyhre-Poulsen P. Neural adaptation to resistance training: changes in evoked V-wave and H-reflex responses. *Journal of Applied Physiology* 92: 2309-2318, 2002.

Ashe J. Force and the motor cortex. *Behavioural Brain Research* 87: 255-269, 1997.

Beck S, Taube W, Gruber M, Amtage F, Gollhofer A, and Schubert M. Task-specific changes in motor evoked potentials of lower limb muscles after different training interventions. *Brain Research* 1179: 51-60, 2007.

Borenstein M, Hedges LV, Higgins JP, and Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods* 1: 97-111, 2010.

Brerro□Saby C, Delliaux S, Steinberg JG, and Jammes Y. Fatigue□induced changes in tonic vibration response (TVR) in humans: Relationships between electromyographic and biochemical events. *Muscle & Nerve* 38: 1481-1489, 2008.

Byrnes ML, Thickbroom GW, Phillips BA, and Mastaglia FL. Long-term changes in motor cortical organisation after recovery from subcortical stroke. *Brain Research* 889: 278-287, 2001.

Byrnes ML, Thickbroom GW, Phillips BA, Wilson SA, and Mastaglia FL. Physiological studies of the corticomotor projection to the hand after subcortical stroke. *Clinical Neurophysiology* 110: 487- 498, 1999.

Carroll TJ, Riek S, and Carson RG. The sites of neural adaptation induced by resistance training in humans. *Journal of Physiology* 544: 641-652, 2002.

Carroll TJ, Selvanayagam VS, Riek S, and Semmler JG. Neural Adaptations to Strength Training: Moving Beyond TMS and Reflex Studies. *Acta Physiologica* 202: 119-140, 2011.

Carson RG, Nelson BD, Buick AR, Carroll TJ, Kennedy NC, and Mac Cann R. Characterizing changes in the excitability of corticospinal projections to proximal muscles of the upper limb. *Brain Stimulation* 6: 760-768, 2013.

Chen R. Studies of human motor physiology with transcranial magnetic stimulation. *Muscle & Nerve* 23: S26-S32, 2000.

Cheney PD, and Fetz EE. Functional classes of primate corticomotoneuronal cells and their relation to active force. *Journal of Neurophysiology* 44: 773-791, 1980.

Christie A, and Kamen G. Cortical inhibition is reduced following short-term training in young and older adults. *AGE* 36: 749-158, 2014.

Clark BC, Issac LC, Lane JL, Damron LA, and Hoffman RL. Neuromuscular plasticity during and following 3 wk of human forearm cast immobilization. *Journal of Applied Physiology* 105: 868-878, 2008.

Clark BC, Mahato NK, Nakazawa M, Law TD, and Thomas JS. The power of the mind: the cortex as a critical determinant of muscle strength/weakness. *Journal of Neurophysiology* 112: 3219-3226, 2014.

Clark BC, Taylor JL, Hoffman RL, Dearth DJ, and Thomas JS. Cast immobilization increases long□interval intracortical inhibition. *Muscle & Nerve* 42: 363-372, 2010.

Classen J, Liepert J, Wise SP, Hallett M, and Cohen LG. Rapid plasticity of human cortical movement representation induced by practice. *Journal of Neurophysiology* 79: 1117-1123, 1998.

Coombs TA, Frazer AK, Horvath DM, Pearce AJ, Howatson G, and Kidgell DJ. Cross-education of wrist extensor strength is not influenced by non-dominant training in right-handers. *European Journal of Applied Physiology* 116: 1757-1769, 2016.

Council NHaMR. A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines. Canberra: National Health and Medical Research Council, 1999.

Davies C, Dooley P, McDonagh M, and White M. Adaptation of mechanical properties of muscle to high force training in man. *Journal of Physiology* 365: 277, 1985.

Del Balso C, and Cafarelli E. Adaptations in the activation of human skeletal muscle induced by short-term isometric resistance training. *Journal of Applied Physiology* 103: 402-411, 2007.

Downs SH, and Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology and Community Health* 52: 377-384, 1998.

Duchateau J, Semmler JG, and Enoka RM. Training adaptations in the behavior of human motor units. *Journal of Applied Physiology* 101: 1766-1775, 2006.

Enoka RM. Muscle strength and its development. New perspectives. *Sports Medicine* 6: 146-168, 1988.

Fimland M, Helgerud J, Solstad G, Iversen V, Leivseth G, and Hoff J. Neural adaptations underlying cross-education after unilateral strength training. *European Journal of Applied Physiology* 107: 723-730, 2009.

Fisher BE, Southam AC, Kuo Y-L, Lee Y-Y, and Powers CM. Evidence of altered corticomotor excitability following targeted activation of gluteus maximus training in healthy individuals. *NeuroReport* 27: 415-421, 2016.

Fuhr P, Agostino R, and Hallett M. Spinal motor neuron excitability during the silent period after cortical stimulation. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section* 81: 257-262, 1991.

Gandevia S, and Burke D. Projection of thenar muscle afferents to frontal and parietal cortex of human subjects. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section* 77: 353-361, 1990.

Garry MI, Kamen G, and Nordstrom MA. Hemispheric differences in the relationship between corticomotor excitability changes following a fine-motor task and motor learning. *Journal of Neurophysiology* 91: 1570-1578, 2004.

Goodwill AM, Pearce AJ, and Kidgell DJ. Corticomotor plasticity following unilateral strength training. *Muscle & Nerve* 46: 384-393, 2012.

Griffin L, and Cafarelli E. Transcranial magnetic stimulation during resistance training of the tibialis anterior muscle. *Journal of electromyography and kinesiology : Official journal of the International Society of Electrophysiological Kinesiology* 17: 446-452, 2007.

Gruber M, Linnamo V, Strojnik V, Rantalainen T, and Avela J. Excitability at the motoneuron pool and motor cortex is specifically modulated in lengthening compared to isometric contractions. *Journal of Neurophysiology* 101: 2030-2040, 2009.

Hallett M. Transcranial magnetic stimulation and the human brain. *Nature* 406: 147-150, 2000.

Hendy AM, and Kidgell DJ. Anodal tDCS applied during strength training enhances motor cortical plasticity. *Medicine & Science in Sports & Exercise* 45: 1721-1729, 2013.

Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, and Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *British Medicine Journal* 343: d5928, 2011.

Higgins JP, Thompson SG, Deeks JJ, and Altman DG. Measuring inconsistency in meta-analyses. *British Medicine Journal* 327: 557–560, 2003.

Howatson G, Taylor MB, Rider P, Motawar BR, McNally MP, Solnik S, DeVita P, and Hortobágyi T. Ipsilateral motor cortical responses to TMS during lengthening and shortening of the contralateral wrist flexors. *European Journal of Neuroscience* 33: 978-990, 2011.

Inghilleri M, Berardelli A, Cruccu G, and Manfredi M. Silent period evoked by transcranial stimulation of the human cortex and cervicomedullary junction. *Journal of Physiology* 466: 521-534, 1993.

Jensen JL, Marstrand PC, and Nielsen JB. Motor skill training and strength training are associated with different plastic changes in the central nervous system. *Journal of Applied Physiology* 99: 1558-1568, 2005.

Kamen G. Reliability of Motor-Evoked Potentials during Resting and Active Contraction Conditions. *Medicine & Science in Sports & Exercise* 36: 1574-1579, 2004.

Karni A, Meyer G, Rey-Hipolito C, Jezzard P, Adams MM, Turner R, and Ungerleider LG. The acquisition of skilled motor performance: fast and slow experience-driven changes in primary motor cortex. *Proceedings of the National Academy of Sciences* 95: 861-868, 1998.

Kidgell DJ, Mason J, Frazer A, and Pearce AJ. I-wave periodicity transcranial magnetic stimulation (iTMS) on corticospinal excitability. A systematic review of the literature. *Neuroscience* 322: 262-272, 2016.

Kidgell DJ, and Pearce AJ. Corticospinal properties following short-term strength training of an intrinsic hand muscle. *Human Movement Science* 29: 631-641, 2010.

Kidgell DJ, and Pearce AJ. What has transcranial magnetic stimulation taught us about neural adaptations to strength training? A brief review. *Journal of Strength & Conditioning Research* 25: 3208-3217, 2011.

Kidgell DJ, Stokes MA, Castricum TJ, and Pearce AJ. Neurophysiological Responses After Short-Term Strength Training of the Biceps Brachii Muscle. *Journal of Strength & Conditioning Research* 24: 3123-3132, 2010.

Kidgell DJ, Stokes MA, and Pearce AJ. Strength training of one limb increases corticomotor excitability projecting to the contralateral homologous limb. *Motor Control* 15: 247-266, 2011.

Kobayashi M, and Pascual-Leone A. Transcranial magnetic stimulation in neurology. *Lancet Neurology* 2: 145-156, 2003.

Kujirai T, Caramia M, Rothwell J, Day B, Thompson P, Ferbert A, Wroe S, Asselman P, and Marsden C. Corticocortical inhibition in human motor cortex. *Journal of Physiology* 471: 501-519, 1993.

Latella C, Kidgell DJ, and Pearce AJ. Reduction in corticospinal inhibition in the trained and untrained limb following unilateral leg strength training. *European Journal of Applied Physiology* 112: 3097-3107, 2012.

Lee M, Gandevia SC, and Carroll TJ. Short-term strength training does not change cortical voluntary activation. *Medicine & Science in Sports & Exercise* 41: 1452-1460, 2009.

Leung M, Rantalainen T, Teo W-P, and Kidgell D. Motor cortex excitability is not differentially modulated following skill and strength training. *Neuroscience* 305: 99-108, 2015.

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, and Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *British Medicine Journal* 339: 2009.

McDonnell MN, Orekhov Y, and Ziemann U. The role of GABAB receptors in intracortical inhibition in the human motor cortex. *Experimental Brain Research* 173: 86-93, 2006.

Moher D, Liberati A, Tetzlaff J, and Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of Internal Medicine* 151: 264-269, 2009.

Muellbacher W, Ziemann U, Boroojerdi B, Cohen L, and Hallett M. Role of the human motor cortex in rapid motor learning. *Experimental Brain Research* 136: 431-438, 2001.

Muellbacher W, Ziemann U, Wissel J, Dang N, Kofler M, Facchini S, Boroojerdi B, Poewe W, and Hallett M. Early consolidation in human primary motor cortex. *Nature* 415: 640-644, 2002.

Müller-Dahlhaus JFM, Orekhov Y, Liu Y, and Ziemann U. Interindividual variability and age-dependency of motor cortical plasticity induced by paired associative stimulation. *Experimental Brain Research* 187: 467-475, 2008.

Narici MV, Roi G, Landoni L, Minetti A, and Cerretelli P. Changes in force, cross-sectional area and neural activation during strength training and detraining of the human quadriceps. *European Journal of Applied Physiology and Occupational Physiology* 59: 310-319, 1989.

Ni Z, and Chen R. Repetitive transcranial magnetic stimulation: faster or longer is not necessarily more. *Journal of Physiology* 586: 3733-3734, 2008.

Pascaul-Leone A, Dang N, Cohen LG, Brasil-Neto JP, Cammarota A, and Hallett M. Modulation of muscle responses evoked by transcrannial magnetic stimulation during the acquisition of new fine motor skills. *Journal of Neurophysiology* 74: 1037-1043, 1995.

Pearce AJ, Hendy A, Bowen WA, and Kidgell DJ. Corticospinal adaptations and strength maintenance in the immobilized arm following 3 weeks unilateral strength training. *Scandinavian Journal of Medicine and Science in Sports* 23: 740-748, 2013.

Petersen NC, Butler JE, Taylor JL, and Gandevia SC. Probing the corticospinal link between the motor cortex and motoneurones: some neglected aspects of human motor cortical function. *Acta Physiologica* 198: 403-416, 2010.

Reis J, Swayne OB, Vandermeeren Y, Camus M, Dimyan MA, Harris□Love M, Perez MA, Ragert P, Rothwell JC, and Cohen LG. Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. *Journal of Physiology* 586: 325-351, 2008.

Rosenkranz K, Kacar A, and Rothwell JC. Differential modulation of motor cortical plasticity and excitability in early and late phases of human motor learning. *Journal of Neuroscience* 27: 12058-12066, 2007.

Rossini P, Barker A, Berardelli A, Caramia M, Caruso G, Cracco R, Dimitrijević M, Hallett M, Katayama Y, Lücking C, Maertens de Noordhout A, Marsden C, Murray N, Rothwell J, Swash M, and Tomberg C. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalography Clinical Neurophysiology* 91: 79-92, 1994.

Sale DG. Neural adaptation to resistance training. *Medicine & Science in Sports & Exercise* 20: S135-S145, 1988.

Sandbrink F. The MEP in clinical neurodiagnosis. In: *The Oxford Handbook of Transcranial Stimulation*, edited by Wasserman EM, Epstein CM, Ziemann U, Walsh V, Paus T, and Lisanby SH. Oxford: Oxford University Press, 2008, p. 237-283.

Sekiguchi H, Nakazawa K, and Suzuki S. Differences in recruitment properties of the corticospinal pathway between lengthening and shortening contractions in human soleus muscle. *Brain Research* 977: 169-179, 2003.

Selvanayagam VS, Riek S, and Carroll TJ. Early neural responses to strength training. *Journal of Applied Physiology* 111: 367-375, 2011.

Taube W, Gruber M, Beck S, Faist M, Gollhofer A, and Schubert M. Cortical and spinal adaptations induced by balance training: correlation between stance stability and corticospinal activation. *Acta Physiologica* 189: 347-358, 2007.

van Hedel H, Murer C, Dietz V, and Curt A. The amplitude of lower leg motor evoked potentials is a reliable measure when controlled for torque and motor task. *Journal of Neurology* 254: 1089-1098, 2007.

Vie B, Gomez N, Brerro-Saby C, Weber JP, and Jammes Y. Changes in stationary upright standing and proprioceptive reflex control of foot muscles after fatiguing static foot inversion. *Journal of Biomechanics* 46: 1676-1682, 2013.

Vucic S, Cheah BC, Krishnan AV, Burke D, and Kiernan MC. The effects of alterations in conditioning stimulus intensity on short interval intracortical inhibition. *Brain Research* 1273: 39-47, 2009.

Weier AT, Pearce AJ, and Kidgell DJ. Strength training reduces intracortical inhibition. *Acta Physiologica* 206: 109-119, 2012.

Werhahn KJ, Kunesch E, Noachtar S, Benecke R, and Classen J. Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. *Journal of Physiology* 517: 591-597, 1999.

Wilson SA, Lockwood RJ, Thickbroom GW, and Mastaglia FL. The muscle silent period following transcranial magnetic cortical stimulation. *Journal of the Neurological Sciences* 114: 216-222, 1993.

Wolters A, Ziemann U, and Benecke R. The cortical silent period. In: *The Oxford Handbook of Transcranial Stimulation*, edited by Wasserman EM, Epstein CM, Ziemann U, Walsh V, Paus T, and Lisanby SH. London: Oxford University Press, 2008, p. 91-102.

Figure Legends

Figure 1: Sample recording of a silent period from the forearm flexors during a low-level contraction (5 ± 2% maximal rmsEMG). Silent period was measured from the onset of the MEP (cursor 1) to the return of EMG (cursor 2).

Figure 2: Five overlayed sweeps of paired-pulse MEPs from the wrist flexors during a low-level contraction (5 ± 2% maximal rmsEMG). The arrows indicate the triggering of paired-pulse stimulation with the first trigger (left waveform) being the single pulse conditioning subthreshold (CS) stimulation, with the second trigger (right waveform) being the suprathreshold (TS) stimulus following the paired-pulse stimulation at a interstimulus interval of 3 ms.

Figure 3: Yield of articles for the motor cortical responses to strength training literature using the PRISMA guidelines.

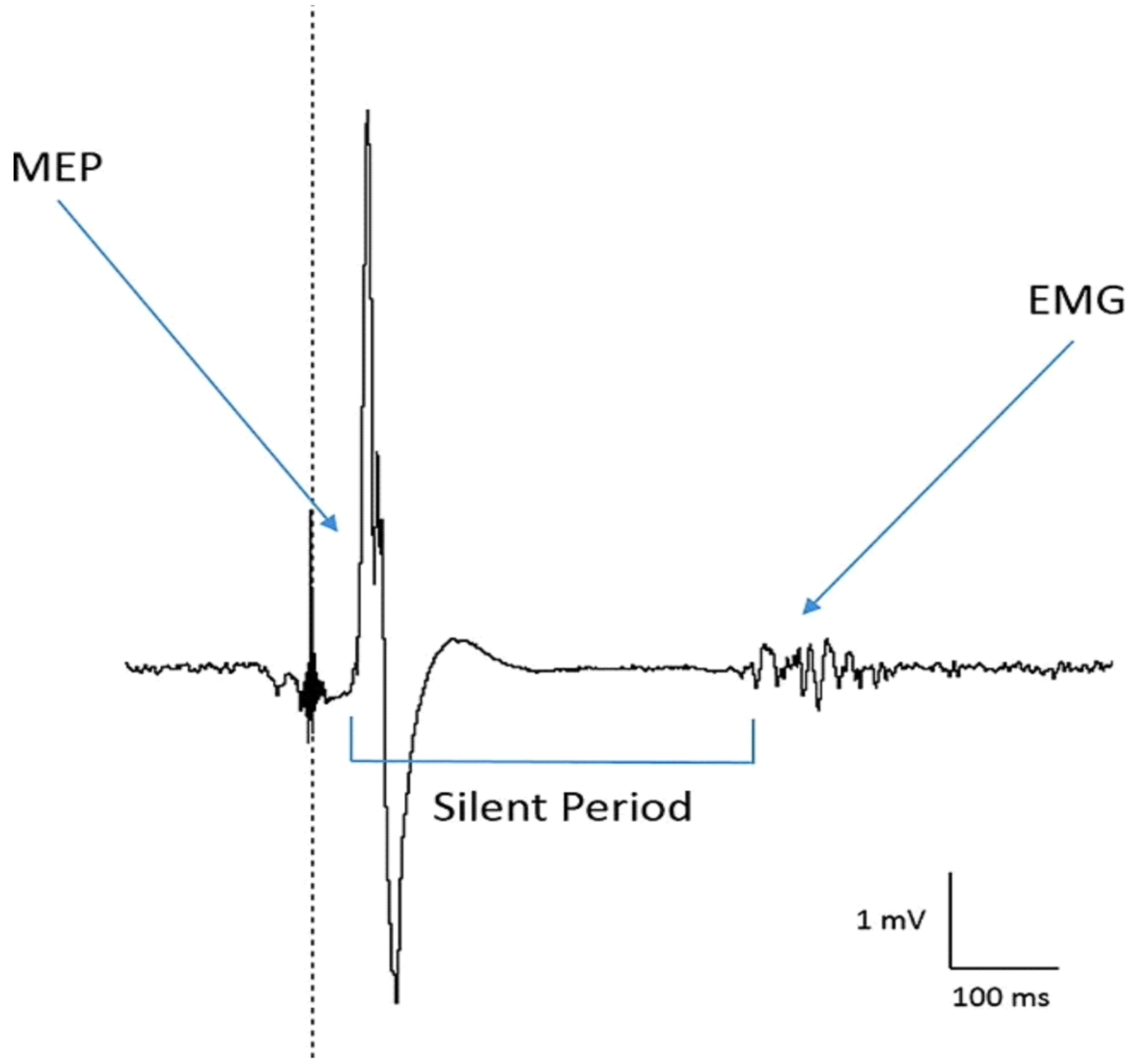
Figure 4: Forest plots for muscle strength following short-term strength training. Pooled effect size for horizontal line = 95% confidence interval. CI: confidence interval, IV: inverse variance.

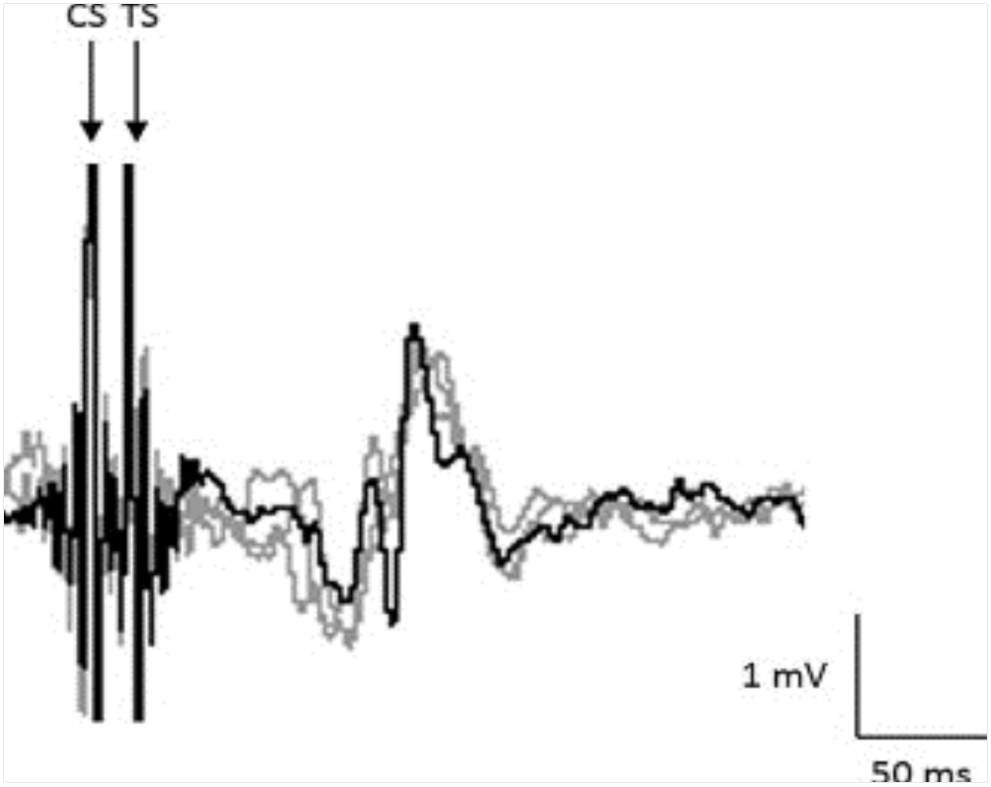
Figure 5: Forest plots for motor threshold following short-term strength training. Pooled effect size for horizontal line = 95% confidence interval. CI: confidence interval, IV: inverse variance.

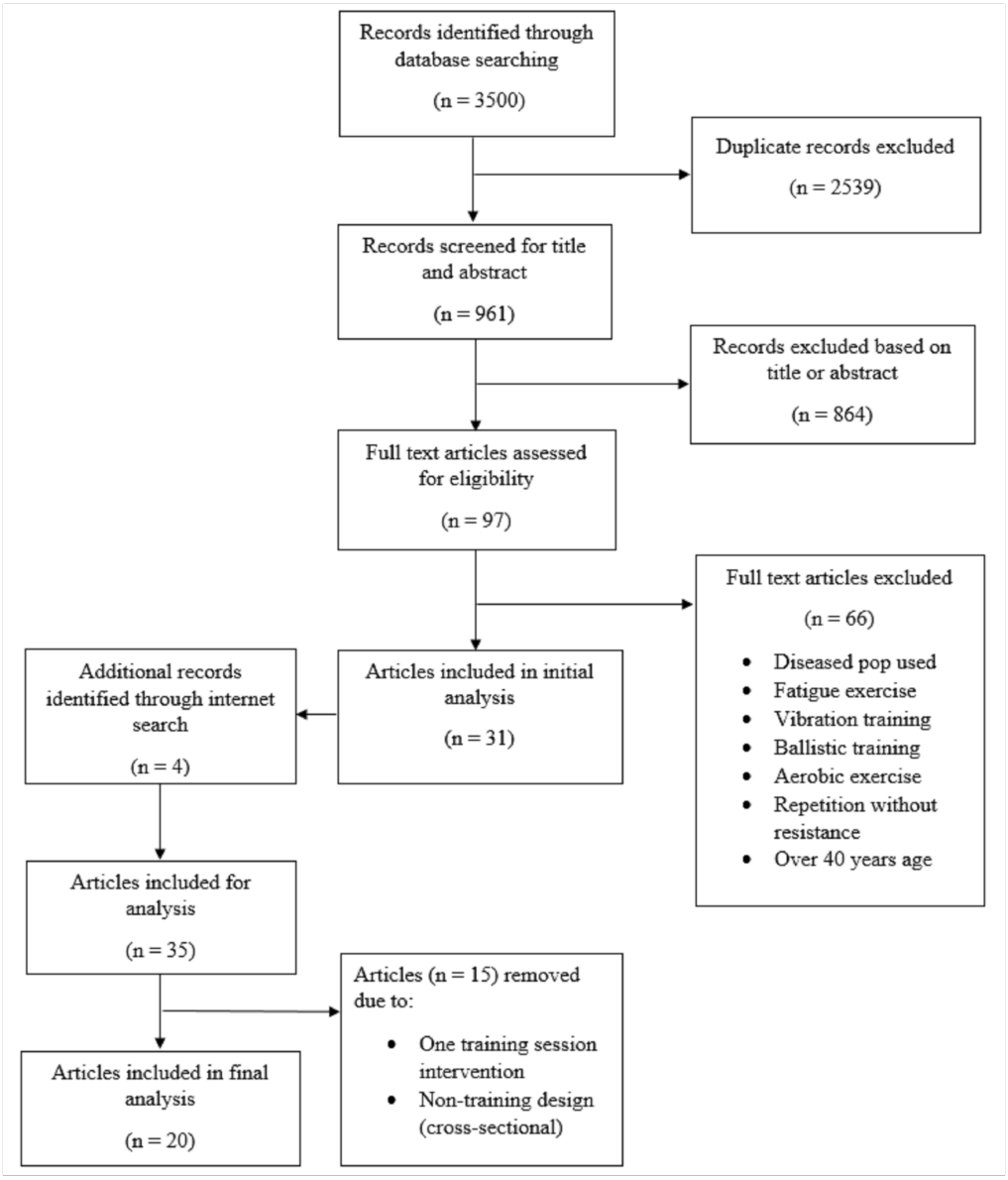
Figure 6: Forest plots for MEP amplitude following short-term strength training. Pooled effect size for horizontal line = 95% confidence interval. CI: confidence interval, IV: inverse variance.

Figure 7: Forest plots for corticospinal inhibition following short-term strength training. Pooled effect size for horizontal line = 95% confidence interval. CI: confidence interval, IV: inverse variance.

Figure 8: Forest plots for short-interval intracortical inhibition following short-term strength training. Pooled effect size for horizontal line = 95% confidence interval. CI: confidence interval, IV: inverse variance.

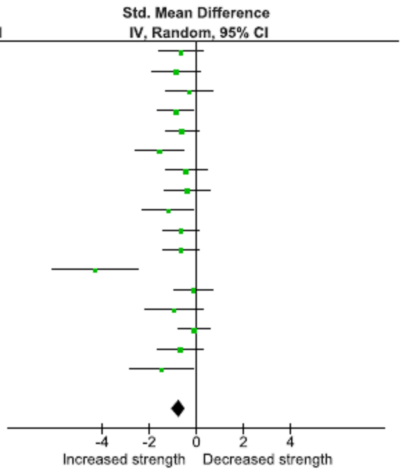

MEP
EMG
Silent Period
1 mV
100 ms

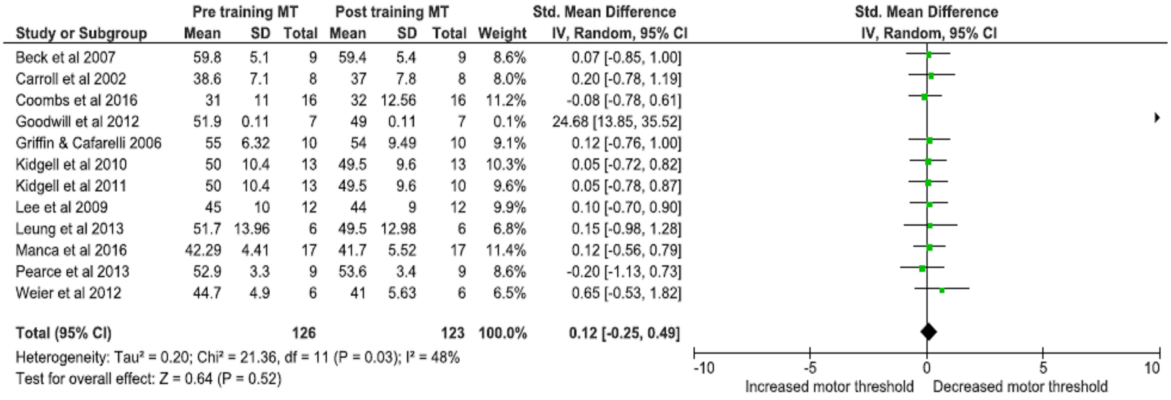

CS
TS
1 mV
50 ms

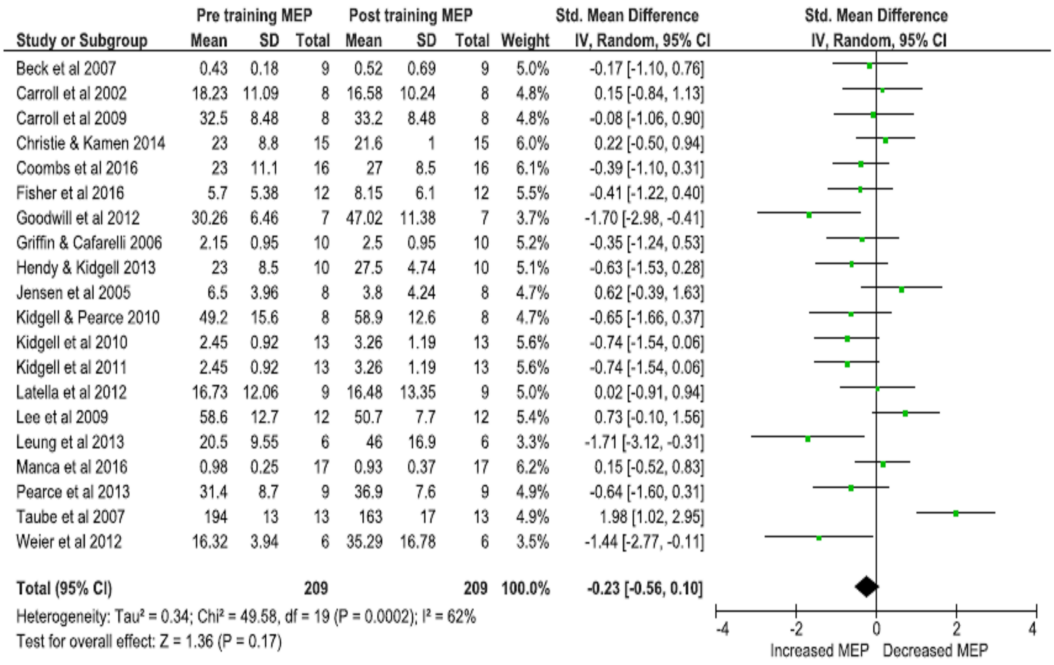

Records identified through database searching
(n = 3500)
Duplicate records excluded
(n = 2539)
Records screened for title and abstract
(n = 961)
Records excluded based on title or abstract
(n = 864)
Full text articles assessed for eligibility
(n = 97)
Full text articles excluded
(n = 66)
Diseased pop used
Fatigue exercise
Vibration training
Ballistic training
Aerobic exercise
Repetition without resistance
Over 40 years age
Additional records identified through internet search
(n = 4)
Articles included in initial analysis
(n = 31)
Articles included for analysis
(n = 35)
Articles (n = 15) removed due to:
One training session intervention
Non-training design (cross-sectional)
Articles included in final analysis
(n = 20)

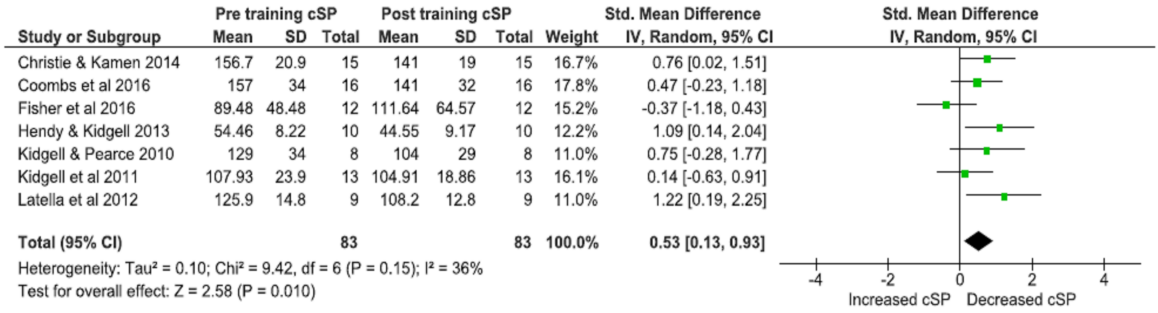
Study or Subgroup	Pre training strength Mean	SD	Total	Post training strength Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Beck et al 2007	11.5	4.5	9	14.8	5.2	9	5.8%	-0.65 [-1.60, 0.31]
Carroll et al 2002	2.21	0.66	8	2.95	0.95	8	5.2%	-0.86 [-1.89, 0.18]
Carroll et al 2009	137.5	33.94	8	148.5	33.94	8	5.6%	-0.31 [-1.29, 0.68]
Christie & Kamen 2014	243.5	48.19	15	285.9	45	15	7.6%	-0.88 [-1.64, -0.13]
Coombs et al 2016	9.3	2.8	16	11	2.7	16	8.0%	-0.60 [-1.31, 0.11]
Griffin & Cafarelli 2006	272.2	26.88	10	321.5	32.57	10	5.3%	-1.58 [-2.61, -0.55]
Hendy & Kidgell 2013	8.95	1.99	10	9.99	2.5	10	6.3%	-0.44 [-1.33, 0.45]
Jensen et al 2005	21.9	7.64	8	24.8	6.51	8	5.5%	-0.39 [-1.38, 0.61]
Kidgell & Pearce 2010	44.48	5.9	8	59.54	15.7	8	4.9%	-1.20 [-2.29, -0.11]
Kidgell et al 2010	11.5	4.5	13	14.8	5.2	13	7.2%	-0.66 [-1.45, 0.14]
Kidgell et al 2011	11.5	4.5	13	14.8	5.2	13	7.2%	-0.66 [-1.45, 0.14]
Latella et al 2012	138	7.2	9	167	5.5	9	2.2%	-4.31 [-6.15, -2.47]
Lee et al 2009	167.1	52.8	12	174	54.2	12	7.1%	-0.12 [-0.93, 0.68]
Leung et al 2013	9.21	3.06	6	12.83	3.85	6	4.2%	-0.96 [-2.19, 0.26]
Manca et al 2016	42.9	11.6	17	43.9	11.1	17	8.4%	-0.09 [-0.76, 0.59]
Pearce et al 2013	17.3	3.2	9	19.7	3.4	9	5.8%	-0.69 [-1.65, 0.27]
Weier et al 2012	86.25	33.17	6	161.25	57.05	6	3.6%	-1.48 [-2.83, -0.14]
Total (95% CI)			**177**			**177**	**100.0%**	**-0.74 [-1.04, -0.45]**

Heterogeneity: Tau² = 0.15; Chi² = 26.76, df = 16 (P = 0.04); I² = 40%
Test for overall effect: Z = 4.98 (P < 0.00001)




Pre training MT
Post training MT
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Beck et al 2007 59.8 5.1 9 59.4 5.4 9 8.6% 0.07 [-0.85, 1.00]
Carroll et al 2002 38.6 7.1 8 37 7.8 8 8.0% 0.20 [-0.78, 1.19]
Coombs et al 2016 31 11 16 32 12.56 16 11.2% -0.08 [-0.78, 0.61]
Goodwill et al 2012 51.9 0.11 7 49 0.11 7 0.1% 24.68 [13.85, 35.52]
Griffin & Cafarelli 2006 55 6.32 10 54 9.49 10 9.1% 0.12 [-0.76, 1.00]
Kidgell et al 2010 50 10.4 13 49.5 9.6 13 10.3% 0.05 [-0.72, 0.82]
Kidgell et al 2011 50 10.4 13 49.5 9.6 10 9.6% 0.05 [-0.78, 0.87]
Lee et al 2009 45 10 12 44 9 12 9.9% 0.10 [-0.70, 0.90]
Leung et al 2013 51.7 13.96 6 49.5 12.98 6 6.8% 0.15 [-0.98, 1.28]
Manca et al 2016 42.29 4.41 17 41.7 5.52 17 11.4% 0.12 [-0.56, 0.79]
Pearce et al 2013 52.9 3.3 9 53.6 3.4 9 8.6% -0.20 [-1.13, 0.73]
Weier et al 2012 44.7 4.9 6 41 5.63 6 6.5% 0.65 [-0.53, 1.82]
Total (95% CI) 126 123 100.0% 0.12 [-0.25, 0.49]
Heterogeneity: Tau² = 0.20; Chi² = 21.36, df = 11 (P = 0.03); I² = 48%
Test for overall effect: Z = 0.64 (P = 0.52)
-10
-5
0
5
10
Increased motor threshold
Decreased motor threshold


Pre training MEP
Post training MEP
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Beck et al 2007 0.43 0.18 9 0.52 0.69 9 5.0% -0.17 [-1.10, 0.76]
Carroll et al 2002 18.23 11.09 8 16.58 10.24 8 4.8% 0.15 [-0.84, 1.13]
Carroll et al 2009 32.5 8.48 8 33.2 8.48 8 4.8% -0.08 [-1.06, 0.90]
Christie & Kamen 2014 23 8.8 15 21.6 1 15 6.0% 0.22 [-0.50, 0.94]
Coombs et al 2016 23 11.1 16 27 8.5 16 6.1% -0.39 [-1.10, 0.31]
Fisher et al 2016 5.7 5.38 12 8.15 6.1 12 5.5% -0.41 [-1.22, 0.40]
Goodwill et al 2012 30.26 6.46 7 47.02 11.38 7 3.7% -1.70 [-2.98, -0.41]
Griffin & Cafarelli 2006 2.15 0.95 10 2.5 0.95 10 5.2% -0.35 [-1.24, 0.53]
Hendy & Kidgell 2013 23 8.5 10 27.5 4.74 10 5.1% -0.63 [-1.53, 0.28]
Jensen et al 2005 6.5 3.96 8 3.8 4.24 8 4.7% 0.62 [-0.39, 1.63]
Kidgell & Pearce 2010 49.2 15.6 8 58.9 12.6 8 4.7% -0.65 [-1.66, 0.37]
Kidgell et al 2010 2.45 0.92 13 3.26 1.19 13 5.6% -0.74 [-1.54, 0.06]
Kidgell et al 2011 2.45 0.92 13 3.26 1.19 13 5.6% -0.74 [-1.54, 0.06]
Latella et al 2012 16.73 12.06 9 16.48 13.35 9 5.0% 0.02 [-0.91, 0.94]
Lee et al 2009 58.6 12.7 12 50.7 7.7 12 5.4% 0.73 [-0.10, 1.56]
Leung et al 2013 20.5 9.55 6 46 16.9 6 3.3% -1.71 [-3.12, -0.31]
Manca et al 2016 0.98 0.25 17 0.93 0.37 17 6.2% 0.15 [-0.52, 0.83]
Pearce et al 2013 31.4 8.7 9 36.9 7.6 9 4.9% -0.64 [-1.60, 0.31]
Taube et al 2007 194 13 13 163 17 13 4.9% 1.98 [1.02, 2.95]
Weier et al 2012 16.32 3.94 6 35.29 16.78 6 3.5% -1.44 [-2.77, -0.11]
Total (95% CI) 209 209 100.0% -0.23 [-0.56, 0.10]
Heterogeneity: Tau² = 0.34; Chi² = 49.58, df = 19 (P = 0.0002); I² = 62%
Test for overall effect: Z = 1.36 (P = 0.17)
-4
-2
0
2
4
Increased MEP
Decreased MEP


Pre training cSP
Post training cSP
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Christie & Kamen 2014 156.7 20.9 15 141 19 15 16.7% 0.76 [0.02, 1.51]
Coombs et al 2016 157 34 16 141 32 16 17.8% 0.47 [-0.23, 1.18]
Fisher et al 2016 89.48 48.48 12 111.64 64.57 12 15.2% -0.37 [-1.18, 0.43]
Hendy & Kidgell 2013 54.46 8.22 10 44.55 9.17 10 12.2% 1.09 [0.14, 2.04]
Kidgell & Pearce 2010 129 34 8 104 29 8 11.0% 0.75 [-0.28, 1.77]
Kidgell et al 2011 107.93 23.9 13 104.91 18.86 13 16.1% 0.14 [-0.63, 0.91]
Latella et al 2012 125.9 14.8 9 108.2 12.8 9 11.0% 1.22 [0.19, 2.25]
Total (95% CI) 83 83 100.0% 0.53 [0.13, 0.93]
Heterogeneity: Tau² = 0.10; Chi² = 9.42, df = 6 (P = 0.15); I² = 36%
Test for overall effect: Z = 2.58 (P = 0.010)
-4
-2
0
2
4
Increased cSP
Decreased cSP

Study or Subgroup	Pre training SICI Mean	SD	Total	Post training SICI Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Beck et al 2007	51	9	9	57	9	9	18.1%	-0.63 [-1.59, 0.32]
Coombs et al 2016	35.13	7.56	16	34.88	7.12	16	19.8%	0.03 [-0.66, 0.73]
Goodwill et al 2012	40.02	13.57	7	30.22	5.21	7	17.0%	0.89 [-0.23, 2.01]
Hendy & Kidgell 2013	20.29	3.8	10	12.46	2.3	10	16.4%	2.39 [1.18, 3.59]
Manca et al 2016	0.47	0.41	17	0.37	0.29	17	19.9%	0.27 [-0.40, 0.95]
Weier et al 2012	47.67	3.72	6	30.77	2.96	6	8.7%	4.64 [2.11, 7.17]
Total (95% CI)			**65**			**65**	**100.0%**	**0.90 [-0.07, 1.86]**

Heterogeneity: Tau² = 1.10; Chi² = 27.69, df = 5 (P < 0.0001); I² = 82%
Test for overall effect: Z = 1.82 (P = 0.07)

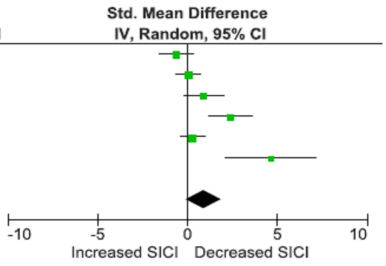


Table 1: Search strategy examples used to yield the motor cortical responses to short-term strength training.

MEDLINE (Ovid)	Scopus
1. Resistance training (inc related terms)	1. (TS=resistance training) AND Language: (English) AND Document types: (Article). Indexes = Sci-Expanded, ESCI, CCR-Expanded, IC Timespan = 1990-2016
2. Limit 1 to (English language and full text and humans and yr="1990-current")	2. (TS=exercise) AND Language: (English) AND Document types: (Article). Indexes = Sci-Expanded, ESCI, CCR-Expanded, IC Timespan = 1990-2016
3. Exercise (inc related terms)	3. (TS=strength training) AND Language: (English) AND Document types: (Article). Indexes = Sci-Expanded, ESCI, CCR-Expanded, IC Timespan = 1990-2016
4. Limit 3 to (English language and full text and humans and yr="1990-current")	4. #3 or #2 or #1. Indexes = Sci-Expanded, ESCI, CCR-Expanded, IC Timespan = 1990-2016
5. Strength training (inc related terms)	5. (TS=transcranial magnetic stimulation) AND Language: (English) AND Document types: (Article). Indexes = Sci-Expanded, ESCI, CCR-Expanded, IC Timespan = 1990-2016
6. Limit 5 to (English language and full text and humans and yr="1990-current")	6. (TS=motor evoked potential*) AND Language: (English) AND Document types: (Article). Indexes = Sci-Expanded, ESCI, CCR-Expanded, IC Timespan = 1990-2016
7. Transcranial magnetic stimulation (inc related terms)	7. (TS=cortical silent period) AND Language: (English) AND Document types: (Article). Indexes = Sci-Expanded, ESCI, CCR-Expanded, IC Timespan = 1990-2016
8. Limit 7 to (English language and full text and humans and yr="1990-current")	8. (TS=intracortical inhibition) AND Language: (English) AND Document types: (Article). Indexes = Sci-Expanded, ESCI, CCR-Expanded, IC Timespan = 1990-2016
9. Motor evoked potential* (inc related terms)	9. #5 and #4
10. Limit 9 to (English language and full text and humans and yr="1990-current")	10. #6 and #4
11. Cortical silent period (inc related terms)	11. #7 and #4
12. Limit 11 to (English language and full text and humans and yr="1990-current")	12. #8 and #4
13. Intracortcial inhibition (inc related terms)	
14. Limit 13 to (English language and full text and humans and yr="1990-current")	
15. #2 or #4 or #6	
16. #8 and #15	
17. #10 and #15	
18. #12 and #15	
19. #14 and #15	